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Bioequivalence Evaluation of Abiraterone 500 mg Tablets Compared with Reference in Healthy Adult Male Subjects Under Fasting Conditions: A Randomized, Replicated Crossover Study.

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ABSTRACT:

Background: Abiraterone acetate is an androgen biosynthesis inhibitor widely used in the management of metastatic hormone-sensitive and castration-resistant prostate cancer. Demonstration of bioequivalence between a generic and reference formulation is essential to support regulatory approval and ensure therapeutic interchangeability. Objective: To evaluate the bioequivalence, safety, and tolerability of Abiraterone 500 mg Tablets compared with ZYTIGA® 500 mg tablets under fasting conditions in healthy adult male volunteers.

Materials and Methods: An open-label, randomized, balanced, two-treatment, two-sequence, four-period, fully replicated crossover bioequivalence study was conducted in healthy adult male subjects. Forty-Eight participants received single oral doses of either the test or reference formulation according to a replicated crossover design under fasting conditions. Blood samples were collected up to 72 hours post-dose for pharmacokinetic assessment. Plasma concentrations of abiraterone were quantified using a validated LC-MS/MS method. Primary pharmacokinetic endpoints included maximum plasma concentration (Cmax) and area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC0-t). Statistical analysis was performed on log-transformed pharmacokinetic parameters using analysis of variance.

Results: A total of 48 subjects were enrolled, and 46 completed all study periods. Mean Cmax values were 107.20 ± 68.42 ng/mL and 121.42 ± 96.56 ng/mL for test and reference products, respectively. Mean AUC0-t values were 509.21 ± 311.84 hr·ng/mL and 548.23 ± 357.35 hr·ng/mL, respectively. The geometric mean ratio for Cmax was 91.56%, with a 90% confidence interval of 82.02–102.22%. The geometric mean ratio for AUC0-t was 95.03%, with a 90% confidence interval of 85.94–105.08%. All pharmacokinetic parameters met predefined bioequivalence acceptance criteria. Both formulations were well tolerated, with no serious adverse events reported.

Conclusion: Abiraterone 500 mg Tablets demonstrated bioequivalence to ZYTIGA® 500 mg tablets under fasting conditions. Both formulations exhibited comparable pharmacokinetic profiles and acceptable safety characteristics, supporting their therapeutic equivalence

Keywords: Abiraterone acetate, Bioequivalence, Pharmacokinetics, Generic drug, Replicated crossover study, LC-MS/MS.

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INTRODUCTION:

Prostate cancer remains one of the most commonly diagnosed malignancies among men worldwide and represents a major contributor to cancer-related mortality. Androgen signaling plays a central role in disease progression, making androgen deprivation a cornerstone of therapeutic management.

Abiraterone acetate is a prodrug that undergoes rapid conversion to abiraterone, a selective inhibitor of cytochrome P450 17A1 (CYP17), an enzyme essential for androgen biosynthesis. By suppressing androgen production in the testes, adrenal glands, and tumor tissues, abiraterone significantly reduces circulating testosterone concentrations and delays disease progression in patients with advanced prostate cancer.

The reference product, ZYTIGA®, has demonstrated substantial clinical benefits in patients with metastatic hormone-sensitive prostate cancer and metastatic castration-resistant prostate cancer. The development of high-quality generic formulations can improve patient access while reducing treatment costs. Regulatory agencies require demonstration of bioequivalence between generic and reference products before approval.

Therefore, the present study was conducted to compare the pharmacokinetic performance of Abiraterone 500 mg Tablets with that of the innovator product ZYTIGA® 500 mg tablets under fasting conditions in healthy adult male volunteers

AIM AND OBJECTIVES

Aim: To establish the bioequivalence of Abiraterone 500 mg Tablets and ZYTIGA® 500 mg tablets following a single oral dose administration under fasting conditions.

Primary Objective: To compare the rate and extent of absorption of the test and reference formulations using pharmacokinetic parameters Cmax and AUC0-t.

Secondary Objectives:

1. To evaluate additional pharmacokinetic parameters including AUC0-inf, Tmax, Kel, and t1/2.
2. To assess the safety and tolerability of both formulations.
3. To determine whether the formulations satisfy regulatory bioequivalence requirements

MATERIALS AND METHODS

Study Design

This investigation was designed as an open-label, randomized, balanced, two-treatment, two-sequence, four-period, fully replicated crossover bioequivalence study conducted under fasting conditions. The replicated design enabled accurate estimation of within-subject variability and supported scaled average bioequivalence assessment for highly variable pharmacokinetic parameters.

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Study Population

Healthy adult male volunteers aged 18–45 years with body mass index ranging from 18.5 to 30.0 kg/m² and body weight of at least 50 kg were enrolled. Participants were required to meet predefined clinical, laboratory, and physical examination criteria prior to inclusion.

Subject Disposition

- Enrolled subjects: 48
- Subjects dosed in Period 1: 48
- Subjects completing study: 46
- Subjects included in pharmacokinetic analysis: 48
- Subjects included in statistical analysis: 48

Study Treatments

Test Product: Abiraterone 500 mg Tablets

Reference Product: ZYTIGA® (abiraterone acetate) 500 mg Tablets.

Each subject received a single oral dose with approximately 240 mL of water under fasting conditions.

Blood Sampling: Twenty-four blood samples were collected during each study period at pre-dose and at multiple time points up to 72 hours after administration.

Bioanalytical Method: Plasma concentrations of abiraterone were quantified using a validated liquid-liquid extraction LC-MS/MS method.

Analytical Parameters

- Lower Limit of Quantification (LLOQ): 0.500 ng/mL
- Calibration Range: 0.500–199.853 ng/mL

Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated using non-compartmental analysis with Phoenix WinNonlin® software.

Primary Parameters

- Cmax, and AUC0-t

Secondary Parameters

- AUC0-inf, Tmax, Kel, t1/2, Residual Area

Statistical Analysis

Log-transformed Cmax and AUC0-t values were analyzed using ANOVA. Geometric mean ratios and corresponding 90% confidence intervals were calculated. Bioequivalence was concluded when confidence intervals fell within predefined regulatory acceptance limits.

RESULTS

Pharmacokinetic Outcomes

Parameter| Test Product| Reference Product

- Cmax (ng/mL)| 107.20 ± 68.42| 121.42 ± 96.56
- AUC0-t (hr·ng/mL)| 509.21 ± 311.84| 548.23 ± 357.35
- AUC0-inf (hr·ng/mL)| 531.82 ± 315.34| 570.65 ± 360.68
- Tmax (h)| 1.50| 1.50
- t1/2 (h)| 13.86 ± 4.66| 13.41 ± 4.31

Statistical Comparison

Parameter| GMR (%)| 90% CI

- Cmax| 91.56| 82.02–102.22
- AUC0-t| 95.03| 85.94–105.08

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The within-subject variability for Cmax exceeded 30%; therefore, widened bioequivalence limits were applied according to regulatory guidance. The observed confidence intervals remained entirely within acceptable limits.

Safety Evaluation: Four adverse events were reported among three subjects during the study. No deaths, serious adverse events, or clinically significant safety concerns occurred. Laboratory assessments, ECG findings, and vital signs remained acceptable throughout the study.

DISCUSSION

The present study compared the pharmacokinetic characteristics of Abiraterone 500 mg Tablets with those of the reference formulation ZYTIGA® under fasting conditions. The replicated crossover design allowed robust estimation of intra-subject variability and facilitated application of scaled average bioequivalence methods for highly variable pharmacokinetic parameters.

The pharmacokinetic profiles of both formulations demonstrated similar rates and extents of absorption. Median Tmax values were identical between treatments, indicating comparable absorption kinetics. Likewise, elimination half-life values were consistent with previously published literature for abiraterone.

The geometric mean ratios for both Cmax and AUC0-t were close to unity, suggesting minimal formulation-related differences. Importantly, the corresponding 90% confidence intervals satisfied regulatory bioequivalence criteria. These findings confirm that the generic formulation delivers systemic exposure equivalent to that of the reference product.

Safety findings further support the acceptability of the test formulation. Reported adverse events were mild and transient, and no clinically significant abnormalities were identified during study participation.

Overall, the study demonstrated that Abiraterone 500 mg Tablets exhibit pharmacokinetic equivalence and comparable safety characteristics relative to ZYTIGA®

CONCLUSION

The present randomized replicated crossover study successfully demonstrated the bioequivalence of Abiraterone 500 mg Tablets and ZYTIGA® 500 mg tablets in healthy adult male subjects under fasting conditions.

The geometric mean ratios and corresponding 90% confidence intervals for the primary pharmacokinetic parameters met predefined regulatory acceptance criteria. Both formulations exhibited comparable absorption, distribution, and elimination characteristics. Safety assessments revealed good tolerability and no serious adverse events.

These findings support the therapeutic interchangeability of Abiraterone 500 mg Tablets

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with the reference formulation and provide evidence for regulatory approval and clinical use.

REFERENCE:

1. International Council for Harmonisation (ICH) E3 Guidelines for Clinical Study Reports.
2. ZYTIGA® (Abiraterone Acetate) Summary of Product Characteristics.

Source of Support: Nil. **Conflicts of Interest:** None